Stabilizing Motifs in Autonomous Boolean Networks and the Yeast Cell-cycle Oscillator

Volkan Sevim[1], Xinwei Gong[2], and Joshua E. S. Socolar[3]

***Short Abstract* — Synchronous Boolean networks are known to have properties that are artifacts of the clocking in the update scheme. Autonomous updating is a less artificial scheme, in which small timing perturbations can occur and attractor stability can be studied. We argue that the stabilization of a limit cycle in an autonomous Boolean network requires a combination of motifs such as coherent feed-forward and repressive feed-back loops that can correct small perturbations to the timing of updates. A recently published model of the yeast transcriptional cell-cycle oscillator [1] contains the such motifs that are necessary for stability under autonomous updating.**

***Keywords* — Autonomous Boolean networks, motifs, stabilization, transcriptional oscillators, yeast cell cycle.**

Synchronously updated Boolean Networks are widely used for modeling Gene Regulatory Networks (GRNs) [2]. However, it has been known that some properties of these networks, such as stabilities of attractors, are artifacts of the clocking in the update scheme [3]. A more realistic scheme, the autonomous update, has been proposed to model gene regulation [3, 4]. In an Autonomous Boolean network, updates are executed in continuous time with each link assigned an independent response delay. This allows one to introduce small perturbations in the update events and thereby study stability of attractors without sacrificing the simplicity of dynamics brought by the Boolean logic.

Using an autonomous Boolean loop with identical but weakly fluctuating response delays for each link, Klemm and Bornholdt showed that some limit cycles are indeed artifacts of the synchronous update as they are only marginally stable in continuous time [3]. Norrell et al. [5] studied a similar simple loop of copiers using a continuous (in both time and space) model. They showed that that a single-pulse attractor on a simple loop can be stabilized using autorepression, if leading edges of pulses propagate faster than the trailing edges.

We argue that stability of a limit cycle in an autonomous Boolean loop requires certain structures, or motifs [6] in the network that can correct small fluctuations in the update timings, which essentially change the durations of traveling pulses. We classify these stabilizing motifs in two classes: rectifiers and growers. A rectifier motif, which can be autorepression, a repressive feed-back or an incoherent feed-forward loop, which sets an upper limit for the durations of the traveling pulses. A grower motif (autoactivation, a coherent feed-forward loop, a diamond) increases the duration of a pulse. A grower and a rectifier added on a simple loop can create stable limit cycles by filtering both pulse-growing and pulse-shrinking perturbations.

We also conduct a numerical study on an autonomous Boolean version of a recently published model of the yeast cell-cycle oscillator [1]. This network contains many intertwined feed-forward and feed-back loops, and the logic functions for the multiple-input nodes are not known. We hypothesize that certain motifs act as growers or rectifiers for stabilizing oscillations. Computer simulations for a range of time delay parameters and different logic configurations indicate that some motifs act as expected in networks that produce stable cycles.

In addition, we extend our numerical study to simple toy oscillators to gain some perspective about mutational robustness and evolvability [7] of such networks. Results indicate that certain motif combinations are more robust to parameter changes than others, and networks with several stabilizing motifs do not necessarily perform better than the simple ones with a single rectifier-grower combination.

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[1,2,3]Department of Physics, Center for Systems Biology, and Center for Nonlinear and Dynamical Systems, Duke University, Durham, NC, USA

E-mail addresses: [1] volkan.sevim@duke.edu, [2] xg6@duke.edu, [3] socolar@phy.duke.edu.

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